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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,809	03/13/2000	Michael P. Murphy	OGA-010.02	6553

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EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/523,809	MURPHY ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68 and 73-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68 and 73-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 5/4/2009 is acknowledged. After entry of the amendment, claims 68 and 73-75 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 68 and 73-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art and State of the art. The art concerning producing an artificial collagen tissue *in vitro* by merely culturing fibroblasts on a porous membrane in a culture medium that must only comprise one of transferrin, ascorbate, or an ascorbate derivative is unpredictable. The state of the tissue engineering art at the time of filing teaches that to engineer living tissues *in vitro*, cultured cells are coaxed to grow on bioactive degradable scaffolds that provide the physical and chemical cues to guide their differentiation and assembly into three-dimensional tissues. The assembly of cells into tissues is a highly orchestrated set of events that requires time scales ranging from seconds to weeks and dimensions ranging from 0.0001 to 10 cm. Coaxing cells to form tissues in a reliable manner is the quintessential engineering design problem that must be accomplished under the classical engineering constraints of reliability. Even though fewer than five engineered tissues have been approved, there are still many technical challenges to overcome before an "off-the-shelf" tissue could be created that represent the translation of scientific discoveries into treatments for patients. Furthermore, the successful large-scale production of engineered tissues requires an adequate source of healthy expandable cells, the optimization of scaffolds, and the creation of bioreactors, which mimic the environment of the body and that are amenable to scale-up. Additional challenges include the preservation of the product so that it has a long shelf-life and the successful use of various approaches to prevent tissue rejection (Naughton et al, Science, 2002, of record).

Like *in vivo* conditions, hormones and growth factors were known to play a role for cell growth and extracellular matrix (ECM) synthesis *in vitro* cell culture systems. Dermal fibroblasts *in vitro* were reported to proliferate and synthesize ECM in response to several hormones or

growth factors. Compared to routine monolayer cultures, dermal fibroblasts in postconfluent cultures were shown to process more efficiently ECM components such as collagen. It has been found that post confluent dermal fibroblasts alone in a special culture condition could form several layers of cells in a culture dish. These findings and the problems of the previous dermal equivalents clearly prompts one skill in the art to develop a safer and more practical alternative dermal equivalent (see Lee DY et al J Dermatol Sci., 2006, Lee et al, Arch Dermatol Res., 2005, of record).

In methods very similar to the instant claims, Parenteau et al (U.S. 5,712,163, of record) teach that the growth of such fibroblasts in culture is routine in the art, but, in order to produce a tissue construct, or a "skin equivalent", the use of serum (and other factors such as insulin, epidermal growth factors, etc.) in the cell culture medium was necessary, and an exogenous ECM component (cells were plated onto a "dermal equivalent) was used (see Examples 1 and 6 in particular). Such serum and exogenous ECM components are excluded by the instant claims.

The state of the art teaches that specialized culture conditions are required for the formation of artificial skin constructs. For example the culture medium for the production of the new dermal equivalent was based on serum containing medium for the routine fibroblast monolayer culture that included EGF, insulin, hydrocortisone, transferrin and triiodothyronine. These supplements are all present and essential in the human body and they are known to support the growth of fibroblasts *in vitro*. EGF stimulates the growth and synthesis of non-collagenous proteins in cultured skin fibroblasts, and its effect on collagen synthesis depends on the culture conditions. Insulin stimulates growth and collagen formation in cultured fibroblasts. Hydrocortisone increases growth as well as collagen and noncollagen protein production in

cultured skin fibroblasts. Transferrin and triiodothyronine were included in some culture medium for culturing fibroblasts. Transferrin stimulates cell proliferation and proteoglycan accumulation of human fibroblasts. Triiodothyronine stimulates the synthesis of proteoglycan in human skin fibroblasts, but decreases the amount of newly synthesized collagen. In addition, serum, which is one of the most important factors that affect the growth and synthetic activities of cells, stimulates collagen production by fibroblasts. Thus, several supplements and serum may work together to influence cell growth and ECM synthesis of dermal fibroblasts, resulting in the formation of the fibrous matrix but the combination of any such conditions would require further extensive and undue amount of experimentation. For example when postconfluent dermal fibroblasts were supplemented with ascorbic acid in a long-term culture a dermis-like matrix was produced. This result can be explained by the finding that ascorbic acid stimulates collagen production in cultured human skin fibroblasts. However, ascorbic acid has a disadvantage in that it is very unstable in solution, especially under the culture conditions of neutral pH and 37 °C. It was also reported that the addition of L-ascorbic acid 2-phosphate rendered fibroblasts to the organization of the dermis-like three-dimensional structure in vitro without any pre-treatments with the plastic dish. It was found that the dermis-like three-dimensional structure by addition of L-ascorbic acid 2-phosphate was much less formed compared to Lee et al products (see Lee DY et al, 2006, of record, and Parenteau et al above).

Furthermore many studies identified the role of various growth factors in cutaneous physiology in order to add cytokines in a timely fashion for optimal tissue engineering of skin. The development process requires a multistep approach for the production of bioengineered skin substitutes, taking into account the effects of various growth factors according to the culture

time. The state of the art clearly emphasize the need for sequential addition of the exogenous factors to the medium used to produce skin substitutes, in order to achieve required structural features and functional properties in-vitro (see Auquer at al, In Vitro Cell Dev Biol Anim., 2000, of record).

Therefore as evidenced above the state of the art clearly teaches that the identification of the "culture conditions" along with the "contents of chemically defined culture media" are the most important aspects required for the development of an artificial skin construct of a clinical relevance, which would enable one skilled in the art to practice the invention as claimed without a further undue amount of experimentation.

In instant case the invention as claimed encompasses producing a cultured artificial collagen/skin construct comprising a layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of serum (or any other "undefined" animal extracts) and exogenous matrix components during any and all culturing conditions. The instant claims fail to recite what are the culturing conditions: for example, culture media contents, growth factors, culture environment that leads to the synthesis of the claimed extracellular matrix components (I and type III collagens, tenascin and any and all glycosaminoglycans to support the growth and proliferation of a second layer of epithelial cells. Similarly the instant claims fail to recite what any specific temporal method steps, but rather recite vague method steps such as "stimulating the fibroblasts", or merely "culturing the fibroblasts…until…" certain desired artificial tissue characteristics are met.

Under the law, the disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). At issue, under the

enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case, in order to identify culture conditions that would lead to the claimed methods and products, one skill in the art would have to engage in excessive and undue experimentation to practice the invention as claimed. Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, (383 U.S. 519, 536, 148 USPQ 689, 696 (1966), stating that in the context of the utility requirement, "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Therefore, the state of the art regarding producing an artificial collagen tissue *in vitro* by merely culturing fibroblasts on a porous membrane in a culture medium that must only comprise one of transferrin, ascorbate, or an ascorbate derivative, is poorly developed. The development of such methods and culture conditions would have to be done empirically, as they are not set forth in the specification.

Number of working examples and Amount of guidance. Applicants have provided no working examples of the claimed methods. All of applicants working examples that relate to the instant claims rely upon cells cultured, at least at some point, under the culture conditions set

forth in Example 1. Example 1 uses newborn calf serum in the culture media, and thus does not provide a working example of the instant claims, which require a culture media "free of undefined animal organ or tissue extracts."

Applicants provide no direction or guidance regarding how to practice the instant invention as claimed. All of the working examples use culture conditions and culture media that are much more narrow in scope than instantly claimed (e.g. the culture media requires a nutrient base (such as DMEM), epidermal growth factor(s), ethanolamine, transferrin, insulin, triiodothyronine, ascorbic acid, glycine, etc.). The specification thus requires the skilled artisan to practice trial and error experimentation with different culture media ingredients, culture conditions, method steps, and human cell lines to determine which (if any) will be compatible and functional as claimed.

Scope of the invention and Nature of the invention. The claims are broad in nature and merely require culturing human fibroblasts on a porous membrane in a chemically defined culture medium such that an artificial collagen tissue is produced: such culture medium only requiring one of transferrin, ascorbate, or an ascorbate derivative. The claimed scope of such culture media is thus very broad (i.e. the claims encompass culturing the cells in, for example, only PBS and transferrin, or only DMEM and ascorbate), and must lead to the creation of an artificial skin material suitable for using in establishing a graft. Therefore, the instant specification, in combination with the prior art, must disclose how to predictably make and use such a broad scope of defined culture media commensurate in scope with the patent protection sought. It does not do so for the reasons set forth above.

The nature of the invention involves the unpredictable art of producing an artificial skin construct *in vitro*.

Level of skill in the art. While the level of skill in the art of growing collagen-like tissue from cell culture fibroblasts using media comprising, *inter alia*, animal serum and exogenous extracellular matrix components is high, the level of skill in the art of doing so in the absence of such serum and exogenous matrix components is low. The unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 75 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection not necessitated by amendment.

Claim 75 recites the limitation "The product" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 75 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. As best understood, claim 75 recites a product prepared by the method of claim 68. Such a product appears to comprise an extracellular matrix comprising certain elements found in naturally occurring collagen, i.e. fibrils, tenascin, and glycosaminoglycans (see Sands (5,618,284) and Holbrook et al (1993), of record). As such, natural collagen, as found in a human being, for example, is within the scope of the claimed product, rendering the claim directed to non-statutory subject matter.

Double Patenting

Claims 68 and 73-75 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 31, 33 and 39-51 of copending Application No. 11/932,052. **This rejection is maintained for reasons made of record in the Office Action dated 2/4/2009, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 5/4/2009 have been fully considered but they are not persuasive. Applicants essentially assert that this rejection be withdrawn because it is the only rejection remaining. This is not convincing because the claims are rejected under other statutes for reasons set forth above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633